Wright nebulizer and the aerosol is administered continuously for two minutes. After each serial concentration, $FEV_1$ values are determined, and the procedure ends when there is a 20% or greater fall in the $FEV_1$ value compared with baseline. Results are expressed as either the provocative dose of methacholine producing a 20% decrease in $FEV_1$ ($PD_{20}$), the cumulative dose in breath units (1 breath unit = 1 inhalation of 1 mg per ml of methacholine) producing a 20% decrease in $FEV_1$, or the area under a dose-response curve. More than 90% of those with asthma respond to methacholine by 200 breath units. Bronchoconstriction following the inhalation of methacholine may also develop in persons with allergic rhinitis, chronic bronchitis, bronchiectasis, and cystic fibrosis, indicating airways hyperreactivity; the provocative or cumulative dose is often larger, however.

Methacholine challenge can be associated with severe bronchoconstriction and should be administered only if oxygen, resuscitation equipment, and inhaled and parenteral bronchodilators are available. It is not a test for routine office use but a useful tool for the evaluation of a person with unexplained respiratory tract symptoms.

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## Management of Chronic Idiopathic Urticaria

URTICARIA (HIVES) IS A PRURITIC MIGRATORY ERUPTION characterized by edematous, erythematous wheals of various sizes in the superficial dermis. The term "chronic" refers to symptoms of six weeks' duration or more. Angioedema is a similar reaction confined to the deeper dermis and subcutaneous tissue. The causes of urticaria and angioedema include food, drugs, infection, inhalants, bites and stings, contactants, physical agents, neoplasms, connective tissue disease, and psychic factors. Fatalities from laryngeal edema have been limited almost exclusively to patients with hereditary angioedema and edema due to Hymenoptera stings. Allergy immunotherapy can also result in death. The cause of chronic urticaria usually is not known, hence the term chronic idiopathic urticaria.

For this discussion it is assumed that possible causes have been considered and avoidance has been attempted. Such avoidance may include a diet free of salicylates, benzoic acid derivatives, and tartrazine yellow No. 5, although their potential role in the etiology is controversial. Additionally, potentiating factors such as alcoholic drinks, aspirin, exertion, and heat generally should be avoided. Most patients respond to symptomatic therapy, of which antihistamines of the $H_1$ inhibitor type are the therapeutic mainstays. Hydroxyzine hydrochloride (Atarax, Vistaril), diphenhydramine hydrochloride (Benadryl), and cyproheptadine hydrochloride (Periactin) are the most effective. Of the three, hydroxyzine is the most potent, with recommended doses starting at 10 to 25 mg four times a day with upward titration. With excessive daytime sedation, 25 to 100 mg can be given at bedtime. Terfenadine (Seldane) with doses as high as 60 mg taken four times during the day can be used in combination with the more sedating $H_1$ antihistamines. Astemizole (Hismanal) just became available in the United States. It has an exceptionally long duration of action. This and another agent under investigation, ketotifen fumarate, might prove to be useful in refractory patients. Combination therapy should be attempted when single agents are insufficient. Cimetidine, an $H_2$ blocker, in combination with the $H_1$ antihistamines, can prove more effective than an $H_1$ antagonist alone in certain patients. Doxepin, an antidepressant with both $H_1$- and $H_2$-blocking properties, is potent in vitro and in vivo and can be given at doses of 25 to 75 mg at bedtime.

Sympathomimetic agents such as terbutaline sulfate, 2.5 to 5 mg three times a day, can supplement the antihistamines. In this respect it should be recalled that patients with acute, severe urticaria or angioedema often respond to subcutaneously administered epinephrine, 0.3 ml of 1:1,000 solution for adults. If the disease is severe and not responding to other forms of treatment, corticosteroids may prove useful. After an initial oral boost such as 45 to 60 mg daily for three to six days, tapering and alternate-day doses, such as 15 to 20 mg every other day, sustain the beneficial effect. Continuous steroid therapy is rarely necessary.

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## Asthmogenic Drugs

ASTHMA IS A MULTIFACTORIAL DISEASE characterized by abnormal bronchial reactivity and may be perceived as wheezing, cough, chest tightness, or shortness of breath. Drugs may affect this hyperreactivity by any of several mechanisms. For example, drugs may alter bronchial reactivity through an immunoglobulin (Ig) E-mediated allergic mechanism or by the direct pharmacologic effect of a drug. We will focus on the second group of adverse reactions because they are repeatedly implicated in provoking occult or quiescent asthma and in increasing the severity of established asthma.

Foremost in this drug class are the $\beta$-adrenergic receptor blockers, which produce bronchoconstriction by directly blocking the $\beta$-receptor on the bronchial smooth muscle. This group currently has three main subclasses in clinical use: nonselective $\beta$-blockers such as propranolol or nadolol; $\beta_1$-selective (cardioselective) $\beta$-blockers—metoprolol, atenolol, for example; and $\beta$-blockers with intrinsic sympathomimetic activity, that is, partial agonists such as pindolol. All three classes have been shown to produce deleterious effects. Clearly, the first class produces bronchospasm at the lowest levels and should be avoided in patients with asthma wherever possible. The second was introduced partly because of this limit within the first class. The degree of effect on the $\beta_1$- versus $\beta_2$-receptors is relative, however, and a large enough dose of a selective drug will still produce significant $\beta_2$-blockade. The properties of the third group are less clear;

reports of a significant effect on pulmonary function conflict with studies that find no adverse effects. With any of the three classes of β-blockers, the need for administering the drug to a patient must be carefully weighed against the clear theoretic and observed untoward effects. An additional caveat is that timolol, a β-blocker used as an eye drop in glaucoma, is capable of inducing an asthmogenic response. Betaxolol hydrochloride (Betoptic), a β-selective eye drop, appears not to have a similar systemic effect and might be a safe substitute.

Aspirin, along with many other nonsteroidal anti-inflammatory drugs, has been shown to produce asthma in selected patients. These agents are presumed to work by inhibiting the synthesis of certain prostaglandins, with subsequent shunting of the parent prostaglandins through alternate pathways. Nonsteroidal anti-inflammatory drugs that are cross-reactive with aspirin include ibuprofen, indomethacin, piroxicam, naproxen, and meclofenamate sodium, along with several others. The asthmogenic effects of aspirin can be seen in between 4% and 10% of asthmatic persons, who should avoid its use, and in a large number of so-called triad patients with asthma, nasal polyposis, and aspirin sensitivity. Rare reports of hydrocortisone succinate producing asthma in aspirin-sensitive patients warrant avoiding its use in these patients. Other steroids seem not to have this effect. There are many previous reports of a cross-reactivity between aspirin and tartrazine dyes, but these have not been rigorously confirmed and may not, in fact, be real.

Angiotensin-converting enzyme inhibitors such as captopril and enalapril maleate have been shown to produce cough as a side effect, which can mimic uncontrolled asthma. The pharmacologic mechanism is uncertain but is thought to be related to bradykinin metabolism and possibly with its role in axonal transmission. These agents are reported to also alter bronchial reactivity, so the cough may indeed be produced by this mechanism. The incidence of cough is low, with estimates varying from 1% to 14%, and is often reported after prolonged use of the drugs.

Incidents of asthma following many other therapeutic interventions are reported on a scattered basis. Mast cell degranulation by an unclear but non-IgE-mediated mechanism can lead to bronchospasm. Examples of drugs that act in this manner include iodinated dye and opiates—especially codeine and morphine. Inhaling acetylcysteine can cause broncho-spasm, presumably by a primary irritant effect. The same has been reported for sympathomimetic aerosols, especially isoproterenol. Rare reports of bronchospasm from cromolyn sodium can be found, and, again, bronchospasm is probably due to primary irritation. Also, agents that alter lower esophageal sphincter tone and increase gastric acid secretion can lead to reflux, which may produce nocturnal cough easily mistaken for asthma.

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